COVID-19 Vaccine Effectiveness in Health Workers (HW)

Expert meeting
Epiconcept
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Objectives VE in HW

- **Primary objective**
  - To measure overall and **product-specific** COVID-19 VE among HW eligible for vaccination against laboratory confirmed SARS-CoV-2 infection

- **Secondary objectives**
  - Report VE estimates by:
    - Vaccination: product, number doses, time since dose
    - Disease severity: asymptomatic v symptomatic v severe
    - SARS-CoV-2 variant
    - Individual: age, gender and health (chronic illness, previous infection)
    - Professional: roles (speciality, ward), activities (type of exposure)

- **Further secondary objectives not addressed in circulated draft protocol**
  - VE against transmission
  - Describe immunogenetic profiles of vaccinated groups

Study design and population

- Study design
  - Prospective cohort study at hospital level
- Study population
  - HW includes all categories (e.g. clinical, ancillary etc) eligible for vaccination
  - Recruitment from hospital settings
  - Enrolment all or random sample HW at each study site

Exposure and outcome

- Exposure: vaccination
  - Definition of vaccinated depends on the vaccine
    - Number doses (fully v partially vaccinated)
    - Date vaccinations
    - Brand
    - Batch
  - Highlights importance of good quality data collection and need to confirm vaccination data

- Outcome
  - Infection: RT-qPCR of naso-pharyngeal samples
    - Alternative sampling (e.g. saliva) to promote regular follow-up
  - Symptomatic disease (mild v severe)
  - Genetic variant

Sample sizes

Follow up 1 year

Hazard rate (/yr)	Total size	N unvac	Event unvac	N vac	Events vac	VC	VE
0.05	**1350**	135	7	1215	6	90	90
	1913	191	9	1722	17	90	80
	3860	386	19	3474	69	90	60
	5842	584	28	5258	130	90	50
	3153	630	31	2523	62	80	50
0.1	**680**	68	6	612	6	90	90
	966	96	9	870	17	90	80
	1356	135	13	1221	36	90	70
	1957	195	19	1762	69	90	60
	2968	296	28	2672	130	90	50
	333	99	9	234	5	70	80
	1179	353	34	826	40	70	50
	1001	400	38	601	29	60	50
0.2	**492**	49	9	443	17	90	80
	694	69	13	625	36	90	70

Stata code: stpower exponential 0.1, power(0.8) loghazard hratio(0.1(0.1)0.5) fperiod(0.25) p1(0

Follow up 3 months

Hazard rate (/yr)	Total sample	N unvac	Events unvac	N vac	Events vac	VC	VE
0.05	**3740**	748	9	2992	7	80	80
	5465	1093	14	4372	16	80	70
	8084	1616	20	6468	32	80	60
	12455	2491	31	9964	62	80	50
	23088	2308	29	20780	129	90	50
0.1	**697**	278	7	419	1	60	90
	1075	430	11	645	3	60	80
	1623	649	16	974	7	60	70
	2472	988	24	1484	15	60	60
	7667	**766**	**19**	**6901**	**69**	**90**	**60**
	11590	1159	29	10431	130	90	50
0.2	**2681**	268	13	2413	36	90	70
	3860	386	19	3474	69	90	60
	5842	584	28	5258	130	90	50

Data Analysis

- Cohort study design
  - Person-time analysis allows individuals to move between "states"
    - Unvaccinated → vaccinated; high ↔ low exposures
  - Poisson regression assumes constant rates over time….
    - Split time and allow for piece-wise different rates
  - Cox regression assumes constant hazard ratio over time (but not hazard)
- Pooling data
  - Use of standardised protocol to pool at regional/national levels
  - Obtain higher precision estimates
  - Multilevel modelling to account for clustering of data by site or country

Follow up

- Enrolment
  - Respiratory specimen
  - Serology
  - Questionnaire: baseline characteristics, vaccination, exposures 14 days before (hospital and community), previous SARS-CoV-2
- Follow up
  - Weekly PCR irrespective of symptoms
  - Weekly questionnaire for changes in symptoms, vaccination status and exposures (professional and personal)
  - Further serology
- Duration of follow-up considering limited time for study
  - Sample size considerations
  - Limited study time (maximum 6 months?)
  - Continuation of cohorts beyond study period

Effect modifiers/confounders:

Essential variables to collect and how to best document

- Demographic: age, sex, ethnic group, socio-economic status
- Chronic conditions and relevant medication
  - Time dependent (i.e. regular update) or collect just at enrolment?
- Blood group?
- Exposures in the hospital/ward (time dependent)
  - Aerosol generating procedures performed
  - Number of COVID patients contacted and average time per patient
  - PPE, IPC indicators (Availability? Use? Both?)
- Exposures in the community (time dependent)
  - Household composition
  - Contact with cases
  - Use of public transport
  - Social events
  - Use of masks

Discussion points (1)

- Objective: Estimate VE infection transmission
  - VE against infection adequate?
    - Reporting of viral load assuming ↑viral load = ↑ risk of transmission
  - Household transmission study to estimate secondary attack rates?
    - Recruitment of (random?) sample of HW and their households
    - Random versus volunteer HW enrolled
    - Distinguish infections acquired from HW and from community
  - Alternative designs?
- Objective: description immunogenetic profiles
  - Sub-study of B and T cell responses in vaccinated populations
  - Key research questions to be addressed
- Objectives: any research questions being overlooked?

Discussion points (2)

- Genetic sequencing of infections to estimate VE by variant
  - Capacity and resource intensive – random selection of samples to sequence
  - Role of study as sentinel surveillance of VE in emerging variants?
- Follow-up of HW
  - Enthusiasm of HW to participate (e.g. high service demand)
  - Duration of follow-up (3-6 months) and acceptability weekly swabbing
    - Current testing regimen and alternatives of self-swabs or saliva
- HW vaccination programme with rapid and high uptake
  - Unvaccinated may have unique characteristics (e.g. previous infection, exposures)
  - HW vaccinated before study initiation (infected between time points)
  - Data collection at T_0 to identify previously infected
    - Serology to discriminate natural and acquired immunity
      - Differential profiles assessed with 2 tests for anti-N and anti-S antibody
    - Questionnaire to collect retrospective symptom information
    - Sensitivity analysis of individuals with evidence of infection

Discussion points (3)

Accounting for biases/effect modifiers/confounders

- Prevent or minimise biases in design and analysis?
  - Known v unknown previous infection
  - Confirmation of vaccination status
  - Differential exposure between vaccinated and unvaccinated
  - Collection of national/site meta data to inform analysis
    - COVID19 incidence in community and study site
    - Site data on PPE availability and use to triangulate self-reported use
  - Differential ascertainment of outcome
    - Reporting of viral load for PCR+
    - Lower viral loads in vaccinated?
- Unmeasured variables?
- Other limitations?